AF

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,348	07/13/2001	Avi Ashkenazi	10466/55	3826

35489 7590 10/21/2005

HELLER EHRMAN LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER	
SAOUD, CHRISTINE J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,348	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Christine J. Saoud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-46 and 49-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-46 and 49-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Claims 44-46 and 49-51 are pending in the instant application. Claims 1-43 and 47-48 have been canceled in a previous amendment.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Applicant's arguments filed 25 July 2005 have been fully considered but they are not deemed to be persuasive.

Claim Rejections - 35 USC § 101

Claims 44-46 and 49-51 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons of record in the previous Office action(s).

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. At pages 3-5 of the response, Applicant reviews the legal standard for patentable utility, with which the Examiner takes no issue.

At pages 5-6, Applicant argues that Pennica and Konopka teach "noting conclusive regarding the absence of correlation between gene amplification and over-expression of mRNA or polypeptides in most genes, in general". Applicant asserts that the Examiner has generalized specific results of Pennica and Konopka to cover all genes. Applicant argues at page 6 that the standard for utility is that it is "more likely than not" that the asserted utility is specific and substantial and that the Office did not present evidence to establish that there is not a reasonably expectation that the encoded polypeptide has utility (*i.e.*, is useful as a diagnostic tool in certain cancers). Applicant argued that the Examiner has not presented a *prima facie* case for lack of utility

These arguments have been fully considered, but are not persuasive. While one can find prior art that supports a "significant probability" that mRNA and protein levels will correlate, there is influential art of record that requires the Examiner maintain that, as a whole, the prior art does not provide a reasonable expectation that expression of the nucleic acid of SEQ ID NO:17 positively correlates with the expression of the protein of SEQ ID NO:18. This is particularly true of genomic DNA. The advent of proteome analysis has begun to elucidate the reality of nucleic acid and protein expression which is becoming recognized as more complicated and different from the previously accepted dogma. As stated in the Office action mailed 02/23/05, "For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a micoarray (p. 408, middle of right column). Hu et al. discovered

that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease." Indeed, there is evidence in the art to refute generalizations about gene/protein correlations. For example, Haynes et al. (Electrophoresis 19: 1862-187l, 1998, previous cited) showed from studies with yeast that among 80 proteins studied which were relatively homogenous in half-life and expression level, no strong correlation existed between protein and transcript levels. It was concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. l 863, second paragraph, and Figure 1). Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see page 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (page 31291, abstract). Therefore, even if increased mRNA levels could be established for PRO232, it does not follow that polypeptide levels would also be amplified. Given how small the amount that DNA copy number of PRO232 increased in tumors and that it increased in only a minority of lung and colon tumors, and the evidence provided by Haynes et al., Hu et al., Fessler et al., Lian et al., Pennica et al. and Konopka et al., one skilled in the art would not have assumed that a small increase in gene copy number would correlate with significantly increased mRNA or polypeptide levels. The level of increase of the

encoding nucleic acid is not disclosed. One skilled in the art would have to do further research to determine whether or not the PRO232 polypeptide levels increased significantly in the tumor samples. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

As was stated above, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a form the skilled artisan could use without significant further research.

At page 6 of the response, Applicant argues that the data presented in the instant specification show that the gene encoding PRO232 was "significantly amplified" and that these values are considered significant based on a Declaration by Dr. Audrey Goddard. The Declaration of Dr. Goddard, filed under 37 CFR 1.132 (25 July 2005) is insufficient to overcome the rejections of the claims based upon 35 U.S.C. §§ 101 and

112, first paragraph as set forth in the previous Office action(s). Applicant directs the Examiner to page 3 of the Goddard declaration that describes the gene amplification technique in the present application and references that attest to the use of this technique in diagnostic and prognostic fashion. This argument has been fully considered but is not deemed persuasive because it evidences that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO232 gene was amplified in 5 lung tumors and 7 colon tumors by 2-5 fold. It is not known whether PRO232 is expressed in corresponding normal tissues, and what the relative levels of expression are. There is no data related to the polypeptide expression levels in any tissue. If the protein is detected in lung or colon tissue, is this an indication of cancer? If the protein is normally found in lung and colon, under what conditions would it be elevated? If the protein is not detected in a lung/colon sample, is this an indication that there is no cancer? If the protein is found in a lung/colon sample, could one conclude that cancer is present? Based on the data presented in the instant specification, which is limited to gene amplification data, one of ordinary skill in the art cannot answer any of these questions, and therefore, could not use the invention as asserted.

In the absence of any of the above information, all that the specification does is present evidence that the gene encoding PRO232 is amplified in a variety of samples and invites the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed "amplification" of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an

increase in transcription rates. It remains that, as evidenced by the prior art of record, the issue is simply not predictable, and the specification presents a mere invitation to experiment.

Furthermore, the Declaration does not provide data such that the Examiner can independently draw conclusions; only Dr. Goddard's conclusions are provided. It is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue (see Hu et al.; cited previously). The instant specification does not demonstrate that the increased copy number of PRO232 in human lung tumors and colon tumors leads to an increased expression of PRO232 polypeptide in these tumors. Therefore, since Applicant does not provide information regarding the level of expression, an activity, or a role in cancer or any other disease for the PRO232 polypeptide, the invention lacks a substantial or well-established utility.

Applicant argues at page 7 that "not all tumor markers are generally associated with every tumor, or even, with most tumors" and that "some tumor markers are useful for identifying rare malignancies". Applicant asserts that significant amplification data for PRO232 is what lends support to its usefulness as a tumor marker. Applicant's arguments have been fully considered, but are not persuasive. First, the Examiner has no disagreement with the statements that not all tumor markers are generally associated with every tumor or that some tumor markers are useful because they are only found in a few tumors. The deficiency of the instant disclosure is that (1) there is no evidence that the claimed protein is associated with tumors of any kind because the

protein was never measured in tumor tissue and (2) the data presented in the instant specification is so sparse, that one of ordinary skill in the art would not be able to reach a conclusion of whether the gene encoding PRO232 is a marker for lung and/or colon cancer. Again, it is not known if the gene encoding PRO232 is present in normal tissue. It is not known if the PRO232 gene is found in a particular cancer versus another. For example, if the PRO232 gene is found in stage III adenocarcinoma, then absence of this gene in a sample would not be diagnosic of any particular condition, because the individual may have stage I, II or some other form of cancer. Furthermore, if the PRO232 gene is found in normal tissue, its presence would not be a marker for cancer. The specification fails to provide enough information for one of ordinary skill in the art to reasonably conclude that the PRO232 gene is a tumor marker and fails to provide any information on the claimed invention, which is the encoded polypeptide.

Applicant at pages 7-10 of the response refers to three articles (Orntoft et al., Hyman et al., and Pollack et al.) as providing evidence that gene amplification generally results in elevated levels of encoded polypeptide. Applicant characterizes characterizes Orntoft et al. as studying transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Applicant characterizes Hyman et al. as comparing DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. Applicant characterizes

Pollack et al. as profiling DNA copy number alteration across 6691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that one average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold increase in mRNA levels. Applicant concludes that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

This has been fully considered but is not found to be persuasive. Orntoft et al. (Molecular and Cellular Proteomics 1:37-45, 2002) could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract.) It would appear that Applicant has provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Hyman (Cancer Research 62:6240-6245) found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner asserts that 2% does not provide a reasonable expectation that the slight amplification of PRO232 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant

specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung and/or colon cancer.

At page 9 of the response, Applicant refers to the declaration of Dr. Polakis, submitted under 37 C.F.R. § 1.132 with the response filed 09 August 2004. Applicant characterizes the declaration as setting forth Dr. Polakis' experience with microarray analysis wherein approximately 200 gene transcripts present in human tumor cells were found to be at significantly higher levels than in corresponding normal human cells. The declaration goes on to state that antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels compared. The declaration states that in approximately 80% of the cases, the researchers found that increased levels of RNA correlated with changes in the level of protein. Applicant concludes that all of the submitted evidence supports Applicant's position that it is more likely than not that increased gene amplification levels predict increased mRNA and increased protein levels, thus meeting the utility standards. This has been fully considered but is not found to be persuasive. As discussed above, in assessing the weight to be given expert testimony, the Examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with

increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PRO232 (i.e., data regarding amplification of PRO232 genomic DNA), and does not disclose any information regarding PRO232 mRNA levels. Furthermore, there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Pennica et al., Konopka et al., Hu et al. (who reviewed 2286 genes reported in the literature to be associates with breast cancer), Haynes et al., Lian et al., and Fessler et al., all discussed *supra*. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so that the examiner could not independently evaluate them. For example, how many of the tumors were lung and/or colon tumors? How highly amplified were the genes that correlated with increased polypeptide levels?

Applicants argue (pages 10-12) that the results of Hu et al. (J. Proteome Res., 2003, previously cited) do not show a lack of correlation between microarray data and biological significance, have statistical flaws and are applicable only to estrongen-postive breast tumors. The argument has been fully considered, but is not persuasive. While there are shortcomings of the technique used by Hu et al., the findings are suggestive of a correlation between expression level and activity. The caution provided in the last paragraph of p. 411 is noteworthy: "It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even

when these expression changes are statistically significant, it is not always clear if they are biologically meaningful." As discussed above, it is not clear that the expression changes listed in the instant specification are statistically significant, and if they are statistically significant, whether they are biologically meaningful. While Hu et al. examined just one kind of cancer, the results taken together with others previously discussed, support the inability of the skilled artisan to make assumptions about the correlation of nucleic acid expression data with expressed protein data.

At page 12 of the response, Applicant argues that the requirement for an asserted utility to be "substantial" means that the claimed invention must have a "practical purpose" which is not a throw-away or insubstantial use, such as the use of a complex invention as landfill. Applicant quotes from M.P.E.P. § 2107 regarding the requirement for a substantial asserted utility. Applicant argues that they have demonstrated at least one reasonable use for the PRO232 polypeptide as a diagnostic marker for detecting or at least classifying lung or colon tumors. Applicant urges that such uses serve a practical purpose which is not a throw-away or insubstantial use. Applicant also objects to the examiner's characterization of the gene amplification as "preliminary data," stating that there is ample support for the Applicant's position that increased gene amplification levels more likely than not predict increased mRNA and polypeptide levels (page 13 of the response). This has been fully considered but is not found to be persuasive. M.P.E.P. § 2107 I states:

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

In the instant case, the asserted utility that PRO232 polypeptides are useful as diagnostic markers for cancer is not substantial in that further research is required to reasonably confirm a real world context of use. In order for PRO232 polypeptide to be useful as a cancer diagnostic, there must be a detectable change in the amount or form of PRO232 polypeptide between cancerous and healthy tissue. In the instant case, the evidence of record indicates that (1) the initial gene amplification assay only showed a positive result for five out of seventeen lung cancer samples and seven out of seventeen colon cancer samples, and did not take into account aneuploidy in cancerous and non-cancerous lung tissue (lack of matched tissue sample control, lack of aneuploidy control), (2) gene amplification does not reliably correlate with increased mRNA levels (Pennica et al., Konopka et al.), and (3) increased mRNA levels do not reliably correlate with increased polypeptide levels (Haynes et al., Lian et al., Fessler et al., Hu et al.). In view of this, the skilled artisan would have viewed the gene amplification results as preliminary with respect to the utility of the encoded polypeptides, and would have had to experiment further to reasonably confirm whether or not PRO232 polypeptides can be used as a cancer diagnostic agent.

At page 13 of the response, Applicant argues that the Examiner applied an improper legal standard; "a heightened utility standard". Applicants argument is not persuasive because the Examiner has never required that the claimed invention have a therapeutic application. The instant specification asserts that targeting the gene product would have therapeutic benefits. However, the evidence of record fails to support this asserted use for the gene product because there has been no established correlation of

the gene product with any disease or condition for which targeting the gene product would be therapeutic. The Examiner was attempting to be thorough and address all of Applicant's assertions of utility for the claimed invention. The rejection sets forth that the assertion of utility is not substantial. The preponderance of evidence supports this position. See Pennica et al., Konopka et al., Hu et al. (who reviewed 2286 genes reported in the literature to be associated with breast cancer), Haynes et al., Lian et al., and Fessler et al. These references, taken into consideration with the disclosure, indicate to the skilled artisan that it is more likely than not that PRO232 polypeptide is not useful as a cancer diagnostic agent.

For all these reasons, the rejection is maintained.

Claims 44-46 and 49-51 also stand rejected under 35 U.S.C. 112, first paragraph for the reasons of record in the previous Office action(s). Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Priority Determination

As the claimed subject matter is found to lack utility and enablement under 35 U.S.C. §§ 101 and 112, first paragraph, respectively, the effective priority date for this application is the instant filing date, 13 July 2001. Applicant's belief that they are

entitled to the filing date of September 17, 1997 is noted, but not persuasive in view of the rejections of record.

Claim Rejections - 35 USC § 102

Claims 44 and 46 stand rejected under 35 U.S.C. 102(b) as being anticipated by Rosenthal et al. (DE 19818619-A1, 28 October 1999) for the reasons of record in the previous Office action(s).

Applicant argues that the claimed priority of the instant application is 17 September 1997, and therefore, the rejection is not proper. This argument is not persuasive in light of the utility rejection and the effective priority of the instant application based on the lack of utility.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on mttr, 8:00-2:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud